

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE**

**IN RE: VALSARTAN, LOSARTAN,
AND IRBESARTAN PRODUCTS
LIABILITY LITIGATION**

This Document Relates to All Actions

MDL No. 2875

Honorable Robert B. Kugler,
District Court Judge

Oral Argument Requested

**DEFENDANTS' REPLY BRIEF IN SUPPORT OF THEIR
JOINT MOTION TO EXCLUDE THE OPINIONS OF
MAHYAR ETMINAN, PHARMD, MSC**

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Rules

Federal Rule of Evidence 702.....*Passim*

Plaintiffs' Opposition to Defendants' Joint Motion to Exclude the Opinions of Mahyar Etminan, PharmD, MSc (the "Opposition" or "Opp."), does nothing to refute or rehabilitate the unsoundness of Dr. Etminan's methodology, which warrants the exclusion of his opinions for at least two reasons. First, Dr. Etminan admittedly did not consider the totality of the pertinent scientific evidence, as epidemiologists are required to do. Instead, he relied almost entirely on one inapposite occupational study, the Hidajat study, and cherry-picked portions of a few other studies that align with Hidajat to, in his own words, create the appearance that he considered more than just Hidajat. Second, Dr. Etminan's opinions about NDEA were based on just one dietary study examining only pancreatic cancer, the Zheng study, and extrapolating the results from that one study about one type of cancer to the other eight types of cancer alleged in this case.

In addition, in the Opposition, Plaintiffs improperly attempt to supplement Dr. Etminan's opinions with untimely and unsupported new opinions – raised for the first time in the Opposition – about cancer latency. Plaintiffs' attempt is procedurally improper. As such, Dr. Etminan should be precluded from offering any such opinions about cancer latency, as they are unsupported, litigation-driven statements by counsel that are outside the scope of his Report and deposition testimony.

For these reasons, and those set forth in Defendants’ opening brief in support of this Motion (“Opening Brief”), the Court should exclude Dr. Etminan’s testimony and opinions.

ARGUMENT

I. THE OPPOSITION UNDERSCORES DR. ETMINAN’S FAILURE TO CONSIDER THE TOTALITY OF THE EVIDENCE.

A. Dr. Etminan’s Near-Exclusive Reliance On The Hidajat Study.

Even in Plaintiffs’ attempt to show that Dr. Etminan considered “every category of evidence,” Plaintiffs are constrained to repeatedly refer to Dr. Etminan’s discussions about the findings and supposed merits of a single study, Hidajat. *See, e.g.*, Opp. at 6, 10-11, 12, 17, 18, 23-26. In doing so, Plaintiffs highlight the inescapable fact that the Hidajat study formed the basis of nearly all of Dr. Etminan’s opinions.¹ While Plaintiffs argue that Defendants’ criticisms of Hidajat are a “weight of the evidence” issue that has no bearing on admissibility, *see* Opp. at 6, 24, 29-30, Plaintiffs miss Defendants’ point about Dr. Etminan’s flawed methodology. Dr. Etminan’s reliance on a single occupational study for virtually all of his opinions defies accepted epidemiological principles. *See* Deposition Transcript of John Fryzek, Ph.D., [Dkt. 1786-3](#), at 108:10-109:1 (explaining that epidemiologists must look at the totality of the evidence). An expert’s failure to adhere to basic principles

¹ Dr. Etminan acknowledged that Hidajat did not examine colorectal cancer. Report ([Dkt. 1717-3](#)) at 18.

in his field of expertise in his methodology is grounds for exclusion under Rule 702. *See Pritchard v. Dow Agro Sciences*, 705 F. Supp. 2d 471, 484-85 (W.D. Pa. 2010), *aff'd*, 430 F. App'x 102 (3d Cir. 2011) (considering “whether the expert ignored or sufficiently addressed epidemiological studies which contradicted his hypothesis” among other factors in considering the reliability of a general causation opinion). Even if Hidajat did not have the shortcomings identified in Defendants’ Opening Brief,² Dr. Etminan’s methodology would still be flawed because he did not consider the totality of the evidence.

Dr. Etminan’s own testimony also undermines Plaintiffs’ claim that he extensively reviewed “every category of evidence.” *See* Opp. at 9. In response to Defendants’ request for documents relied on in his Report in connection with his deposition, Dr. Etminan produced only a limited number of occupational and dietary studies and just two animal studies. He then testified as follows:

Q: The articles that you provided in response to these requests, include some of the articles and papers that are cited in your report but not all of the articles and papers that are cited in your report.

² While Plaintiffs defend Hidajat as “absolutely on point”; and “the strongest and most comprehensive evidence of NDMA carcinogenicity in humans to date” (Opp. at 6), Plaintiffs are wrong. Hidajat has many limitations identified by the authors themselves, including a failure to control for smoking, a known human carcinogen, possible measurement error due to generalizations, and assumptions made in estimating levels of exposure numerous potentially carcinogenic substances in rubber factory workers. Opening Brief at 15-18.

THE WITNESS: Yeah, **so if there were citations in the report where I only looked at the abstract of the paper and not really included the body of the paper** because I didn't need to, those articles are just cited in my report. But I provided the articles that actually contributed to the weight of the evidence and my opinions in the report.

Deposition Transcript of Mahyar Etminan, Vol. I, [Dkt. 1717-4](#), at 15:25-16:22

(emphasis added).

He further testified that he included occupational studies other than Hidajat in his Report “briefly” and as “background” even though they did not meet his selection criteria *specifically to avoid* suggestions that he only considered Hidajat:

Q: Okay. You included McElvenny in -- why did you include McElvenny in your report?

MR. NIGH: Form objection.

THE WITNESS: I -- **I wanted to also just briefly touch on other occupational studies as well, because if I hadn't, then there would be a question of, you know, why did you -- why did you only look at Hidajat.** So I wanted to mention that there are these occupational studies as well, **but my focus was on the study by Hidajat because it met the main inclusion criteria for my question.**

Q: Did the McElvenny study -- article, though, meet your exclusion criteria?

A: It may have because they did not include NDMA. And again, I just mentioned that it's not in my main analytical framework of evidence when I'm deciding on the causal question. **But I just thought to introduce, you know, just to mention it as background that there - - you know -- and it is part of Hidajat -- in a way related to Hidajat.** It's an older version of Hidajat, so I thought I should mention it.

Etminan Dep., Vol. I, [Dkt. 1717-4](#), at 53:20-54:17 (emphasis added).

Rather than refute Defendants’ criticisms, Plaintiffs’ attempts in their Opposition to overcome Dr. Etminan’s failure to consider all relevant evidence only serves to highlight it. For example, Plaintiffs quote Dr. Etminan’s discussion of the Straif occupational study as proof that he reviewed and considered literature that did not support his ultimate conclusions. Opp. at 11. However, Dr. Etminan himself described that section of his Report as purely a discussion of the study’s “shortcomings,” *i.e.*, an explanation of his reasons for discounting Straif’s “negative” findings in favor of Hidajat’s. Opp. at 10. And, as explained above, Dr. Etminan testified that Straif was only included in his report for background – not because he properly considered it.

Next, Plaintiffs attempt to defend Dr. Etminan’s decision to disregard the valsartan-specific studies by pointing to their purported limitations in estimating exposure levels. Opp. at 18-21. Importantly, if that were the true basis for Dr. Etminan’s exclusion of those studies, Dr. Etminan would have also had to exclude Hidajat, which suffers from significant exposure estimate issues. *See* Etminan Dep., Vol. I, [Dkt. 1717-4](#), at 50:3-51:5. This is yet another example of Dr. Etminan’s flawed methodology in failing to consider studies that contradicted his conclusions based on Hidajat.

Despite Plaintiffs' efforts, Dr. Etminan's misplaced reliance on Hidajat is apparent and pervasive in his testimony and Report. This renders his methodology unreliable and his opinions subject to exclusion.

B. Dr. Etminan Did Not Employ The Same Intellectual Rigor As In His Clinical Work.

Contrary to Plaintiffs' claims, Dr. Etminan conceded that he did *not* employ the same level of intellectual rigor in preparing his Report as he would in his other professional work, particularly in disregarding well-accepted standards of statistical significance. As part of his research work, Dr. Etminan submits studies for publication in peer-reviewed journals. Rep. at 5. When questioned about his inclusion of a non-statistically significant finding in his Report, Dr. Etminan testified as follows:

Q: Okay. If you were to present data to a peer --

THE COURT REPORTER: To appear what?

BY MR. GALLAGHER:

Q: To a peer-reviewed journal, like this where the confidence interval includes 1.0.

A: Uh-huh.

Q: Would you expect that peer-reviewed journal would not let you say that there was statistically significant association?

MR. NIGH: Form objection.

THE WITNESS: Again, it -- it depends the journal on the editorial board. The statistical significant, sort of, misnomer, if you will, that I talked about, is relatively recent. And the American Statistical

Association put out this correction on the interpretation of this -- this topic in 2016. So it will take a while before most editorial boards and editors really come to grasp of what -- what this concept means. **So, again, because up until now, a lot of these editors are sort of interested in statistical significance versus nonstatistical significance.** It's possible that some journals still ask that.

Etminan Dep., Vol. I, [Dkt. 1717-4](#), at 61:19-62:19.

Plaintiffs attempt to harmonize Dr. Etminan's admission that statistical significance remains the standard for peer-reviewed scientific literature with his citation to non-statistically significant findings by simply arguing "the non-statistically significant studies further support and complement the statistically significant studies." Opp. at 13. This only proves, however, that Dr. Etminan failed to apply well-recognized standards and simply cherry-picked non-statistically significant findings, so long as they supported the conclusions in Hidajat.

Dr. Etminan did not apply the same intellectual rigor or methods that would be required for peer-reviewed publication, and his opinions do not meet the Rule 702 standard.

C. Plaintiffs Selectively Quote Dr. Etminan's Report to Save His Bradford Hill Analysis.

Plaintiffs incorrectly argue that Dr. Etminan cannot be excluded for misapplying Bradford Hill because that goes to the weight of the evidence. Contrary to Plaintiffs' argument, an expert may and should be excluded under Rule 702 for failing to reliably apply an accepted methodology, such as Bradford Hill. For example, in *In Re Zolof*, the Third Circuit affirmed exclusion of a plaintiffs' general

causation expert, a statistician who applied the Bradford Hill criteria, on the basis that he had not reliably applied an accepted technique:

Here, we accept that the Bradford Hill and weight of the evidence analyses are generally reliable. We also assume that the “techniques” used to implement the analysis (here, meta-analysis, trend analysis, and reanalysis) are themselves reliable. However, we find that Dr. Jewell did not 1) reliably apply the “techniques” to the body of evidence or 2) adequately explain how this analysis supports specified Bradford Hill criteria. Because “any step that renders the analysis unreliable under the Daubert factors renders the expert's testimony inadmissible,” this is sufficient to show that the District Court did not abuse its discretion in excluding Dr. Jewell's testimony.

In re Zolofit (Sertraline Hydrochloride) Prod. Liab. Litig., 858 F.3d 787, 796-797 (3d Cir. 2017).

Defendants’ opening brief sets forth in detail the shortcomings in Dr. Etminan’s Bradford Hill analysis. Opening Brief at 22-25. In response, Plaintiffs argue Dr. Etminan’s discussion of dose response – which is admittedly based on Hidajat – demonstrates that he properly conducted his entire Bradford Hill analysis. As Defendants’ epidemiology expert Dr. John Fryzek noted during his deposition, “you can’t just look at an individual study. You have to look at the totality of the evidence.” Fryzek Dep., [Dkt. 1786-3](#), at 234:18-235:2. An analysis of just one Bradford Hill criterion, largely based on one study, Hidajat, is not a proper application of the Bradford Hill method. Dr. Etminan’s misapplication of a widely accepted methodology warrants exclusion of his opinions under Rule 702.

II. PLAINTIFFS MISLEAD THE COURT CONCERNING DR. ETMINAN'S METHODOLOGY IN REACHING HIS NDEA OPINIONS.

As set forth in more detail in Defendants' Opening Brief, Dr. Etminan did not even purport to use any reliable methodology to render his opinions that NDEA causes each of the nine cancers alleged in this suit. Instead, he relied entirely on one study examining an association between NDEA and one type of cancer (pancreatic), the Zheng study. He then extrapolated the finding in that study to all other alleged cancers, concluding, based only on the Zheng study, that "it would be expected that NDEA also has the potential to cause the other 8 cancers." Opp. at 27-28 (quoting Rep. at 32).

While Plaintiffs would have the Court believe that Dr. Etminan devoted an entire section in his report to evaluating NDEA carcinogenicity with ample evidence, in fact, Dr. Etminan makes no attempt to explain the connection between NDEA animal studies and the specific cancers alleged in humans in this case. *See* Report at 32. In actuality, Dr. Etminan took the unreliable opinions he formed about NDMA and argued they should also apply to NDEA. That is insufficient to satisfy Rule 702, and Dr. Etminan's opinions regarding NDEA are patently unreliable and must be excluded.

III. THE COURT SHOULD DISREGARD PLAINTIFFS' UNSUPPORTED STATEMENTS AND OPINIONS NOT FOUND IN DR. ETMINAN'S REPORT.

In an untimely attempt to overcome the obvious shortcomings with Dr. Etminan's Report and methodology, Plaintiffs improperly attempt to inject their own unsupported scientific opinions into their Opposition. The Court should not consider these untimely and improper statements in deciding the admissibility of Dr. Etminan's opinions under Rule 702.

First, Plaintiffs falsely claim "Dr. Etminan . . . explains that due to individual variability, cancer latency can have a wide range, **resulting in some individuals developing cancer in a matter of months after NDMA exposure**, while others could take many years to develop cancer." Opp. at 22. Plaintiffs do not cite any authority for this statement, which directly contradicts Dr. Etminan's Report and testimony. In fact, Dr. Etminan testified that a study period of four or five years was too short to determine whether nitrosamines in valsartan caused an increased risk of cancer. Etminan Dep., Vol. II, [Dkt. 1717-5](#), at 52:9-17. He also disregarded the valsartan-specific studies, Gomm and Pottegard, due to "inadequate cancer latency or the time required for the cancer process to complete and lead to symptomatic disease. Report at 31. The Court should not consider Plaintiffs' unsupported contentions that are directly contradicted by their own expert.

Next, Plaintiffs state without basis that “Hidajat provides evidence as to what organs are susceptible to cancer formation if orally ingested NDMA clears the liver and reaches systemic circulation.” Opp. at 25. This was not stated anywhere in Dr. Etminan’s report, nor was it the opinion of Defendants’ expert, Dr. Bottorff,³ whom Plaintiffs selectively quote to give the false impression that his opinions align with the Plaintiffs’ experts on this point.⁴ The Court should similarly disregard this

³ Q: Well, regardless of the dose, if [NDMA] was found in the blood, that means it got past the liver, right?

MS. THOMPSON: Objection. Form.

THE WITNESS: Not necessarily. It could have gotten there from another source.

Q: Such as?

A: There’s known endogenous production of NDMA. So that’s possible. It could have been an environmental exposure that led to NDMA that you found.

Q. What about if someone orally ingests NDMA, and after orally ingesting it, the levels of NDMA in their blood go up?

MS. THOMPSON: Objection to form.

THE WITNESS: Then that would imply to me that the dose is far exceeding the doses that we are talking about here.

Deposition Transcript of Michael Bottorff, Ph.D., [Dkt. 1789-3](#), at 153:5-154:4.

⁴ To make this argument, Plaintiffs willingly misrepresent that a quote from a 1980 study used as an exhibit at Dr. Bottorff’s deposition is actually Dr. Bottorff’s testimony:

MR. VAUGHN: Tyler, can we pull Pegg back up again, the 1980 Pegg study. Let’s go to Page 15 again. Doctor, that second paragraph that starts with the word “finally,” can you read that aloud for the jury?

A. :Finally, it has been reported that NDMA and NDEA were present in human peripheral blood samples and that the amounts increased after a meal. Calculations of total daily exposures have been made on the basis of these figures but without knowledge of the clearance rate these calculations may be seriously in error and may underestimate total exposure.”

unsupported conclusion and litigation-driven statement concerning “systemic circulation” of orally ingested NDMA and NDEA.

To minimize the impact of Dr. Etminan’s failure to consider endogenous NDMA formation or background exposure in his methodology, Plaintiffs argue that “endogenous formation of NDMA should be fairly uniform from one individual to another” and “none of the epidemiological studies measured endogenous NDMA formation.”⁵ Opp. at 26. These statements have no support in Dr. Etminan’s Report. Instead, Dr. Etminan admitted that endogenous formation involves a number of complex variables not addressed by his Report:

Q: Okay. Why don’t we turn to Page 472 of this article?

So, Dr. Etminan, you say that there’s a lot of complex factors that can influence endogenous NDMA; is that right?

A: Yes.

Q: Okay. And that’s why you didn’t include it in your report or address it because it was complex?

Q: And so this is saying just one meal is able to clear the liver and get into the bloodstream, the NDMA; is that correct?

MS. THOMPSON: Objection. Form.

THE WITNESS: Again, I’d have to look at those studies to see if just that one-sentence summary would be an accurate representation.

Bottorff Dep., [Dkt. 1789-3](#), at 257:12-258:17.

⁵ To the extent Plaintiffs would argue that estimation is not equivalent to “measurement,” Hidajat only estimated, and did not measure, NDMA exposure, as did all of the dietary and occupational studies mentioned in the Report.

A: I mean, again, it's very hard to quantify and discuss it in most of the studies that I looked at it, and there's a lot of them. It wasn't really mentioned or measured, so for the whole host of reasons, that's why I mainly focus on exogenous NDMA.

Etminan Dep., Vol. I, [Dkt. 1717-4](#), at 114:19-115:8.

Dr. Etminan also admitted the Jakszyn study, which he claimed to have reviewed, specifically examined endogenous formation of NDMA. Etminan Dep., Vol. I, [Dkt. 1717-4](#), at 117:12-117:22 (Q: So the title of this article by Jakszyn is "Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition Study." Is that right? A: Yes. Q: So in this study, they did try to evaluate -- to measure and evaluate the potential impact of endogenous N-nitroso compounds, right? A: Yeah, seems like it.) Thus, as Dr. Etminan acknowledged, Plaintiffs' assertion that none of the studies he reviewed involved an analysis of endogenous nitrosamine formation is false.

The Court should disregard statements in the Opposition that are not set forth in, inconsistent with, or unsupported by Dr. Etminan's opinions and Report, and preclude Dr. Etminan from offering any opinions about such statements, as they are beyond the scope of Dr. Etminan's Report and deposition testimony and therefore procedurally and substantively improper.

CONCLUSION

For the foregoing reasons, and those discussed in Defendants' opening brief, the Court should exclude the opinions of Dr. Etminan, and preclude him from offering opinions based on Plaintiffs' improper and untimely attempt to supplement his report with assertions regarding cancer latency in their Opposition.

Dated: January 6, 2022

By: /s/ Seth A. Goldberg

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on January 6, 2022, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to all CM/ECF participants in this matter.

/s/ Seth A. Goldberg
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